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A Study on the Preparation, Submission, and Regulatory Review of Electronic Common Technical Documents (eCTD) for Global Markets

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ABSTRACT:
This study examined the preparation, submission, and regulatory review of electronic Common Technical Documents (eCTD) across global markets. The findings highlight that while the CTD and eCTD frameworks (ICH M4 and M8) have significantly advanced global harmonization, substantial regional differences in Module 1 requirements remain. These variations often result in duplication of work and increased resource requirements for multinational pharmaceutical companies. The comparative analysis of eCTD requirements across regulatory authorities (USFDA, EMA, PMDA, Health Canada, and CDSCO) revealed both convergence and divergence in dossier preparation and review. Modules 2–5 follow ICH standards consistently, ensuring that quality, non-clinical, and clinical data remain uniform. However, Module 1 demonstrates significant regional variation, leading to additional workload for companies pursuing global submissions. For instance, USFDA requires patent certification data, EMA emphasizes country-specific annexes, and PMDA requires Japanese translations. These differences, though regionally justified, reduce the harmonization that eCTD was intended to promote. Moreover, technical validation requirements especially XML granularity and hyperlinking—vary slightly, further complicating multinational submissions. Thus, the similarities facilitate a shared foundation for global submissions, but the differences create duplication, potential delays, and higher compliance costs.
Keywords: CTD, eCTD, USFDA, EMA, PMDA

Introduction

Pharmaceutical product development is an elaborate process that requires stringent regulatory oversight to ensure the safety, efficacy, and quality of medicinal products. Once a drug candidate has successfully passed through preclinical and clinical development, the next critical step is to submit a regulatory dossier for marketing authorization. Traditionally, such submissions were conducted using paper-based systems, which often led to inefficiencies, redundancies, and increased costs due to large volumes of documentation [1-3]. To address these challenges, regulatory authorities and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) developed the Common Technical Document (CTD) format in 2000. The CTD provided a standardized structure across five modules, covering administrative information, quality data, non-clinical and clinical studies. The adoption of CTD was a landmark development as it promoted uniformity in dossier preparation, facilitated simultaneous submissions across multiple markets, and reduced duplication of efforts [4].

However, the growing complexity of drug development and the increasing global demand for efficient regulatory processes necessitated further innovation. This gave rise to the electronic Common Technical Document (eCTD**)**, a digital evolution of the CTD, which leveraged electronic data management systems to streamline submissions and lifecycle maintenance. The eCTD format enables not only the initial submission of applications but also updates, amendments, and variations in a structured, electronic manner, ensuring smoother interactions between applicants and regulators.

Need for Global Harmonization [5-7]

Despite the global acceptance of CTD and eCTD, regional variations still exist, leading to challenges for pharmaceutical companies aiming to register their products in multiple markets. The role of ICH has been pivotal in bridging these differences by providing harmonized technical requirements for quality, safety, and efficacy data. ICH guidelines such as M4 (CTD structure) and M8 (eCTD specification) are central in defining the standards for dossier preparation and submission.

Nevertheless, each regulatory authority has specific requirements. For instance:

- The USFDA mandates eCTD submissions via its Electronic Submissions Gateway (ESG) and requires adherence to its regional Module 1 specifications.
- The European Medicines Agency (EMA) enforces eCTD submissions through the Common European Submission Platform (CESP) with additional country-specific requirements within the EU.
- The Pharmaceuticals and Medical Devices Agency (PMDA, Japan) incorporates its own regional variations within Module 1.
- Health Canada requires eCTD submissions through its Regulatory Enrolment Process (REP) and has unique technical validation criteria.
- The Central Drugs Standard Control Organization (CDSCO, India) is currently piloting eCTD acceptance

and gradually transitioning towards mandatory electronic submissions.

This diversity underscores the urgent need for regulatory convergence and global harmonization to minimize duplication of efforts, reduce submission timelines, and facilitate quicker patient access to innovative therapies.

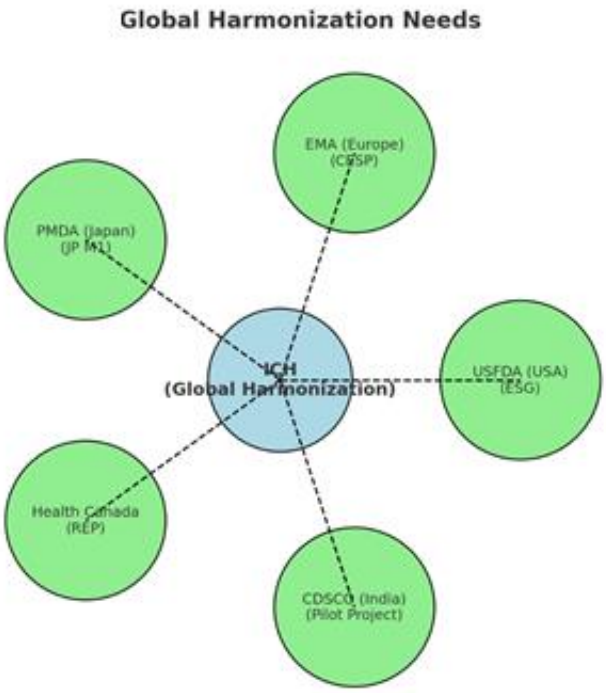

Fig.1: Global Harmonization Needs

Significance of eCTD in Global Markets [7-9]

The eCTD format has revolutionized regulatory submissions by enhancing efficiency, transparency, and consistency. Key advantages include:

- **Efficiency in Submissions**: Automated compilation, hyperlinking, and validation significantly reduce preparation and processing time.
- **Review Timelines**: Structured submissions facilitate faster review by regulatory authorities, enabling quicker approval and market entry.
- **Lifecycle Management**: Unlike paper-based dossiers, eCTD allows for seamless integration of amendments, variations, and responses to regulatory queries within the same submission lifecycle.

However, multinational submissions face challenges such as:

- **Technical Barriers**: Variations in XML backbone requirements, granularity, and regional Module 1 specifications.
- **Regulatory Divergence**: Differences in timelines, acceptance of eCTD versions, and interpretation of ICH guidelines.
- **Resource Constraints**: Smaller companies may lack the financial or technical infrastructure to adopt advanced eCTD preparation and validation tools.

Thus, while eCTD adoption has streamlined global submissions, inconsistencies across markets continue to hinder the realization of a fully harmonized regulatory environment.

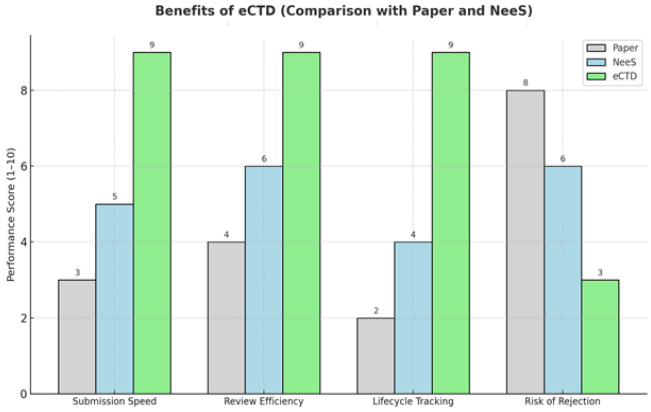

Fig.2: Benefits of eCTD

Methodology

Research Design

The present study adopts a descriptive and comparative research design. A descriptive approach is suitable for outlining the structural and technical features of the electronic Common Technical Document (eCTD), while a comparative framework is essential for analyzing differences and similarities among regulatory agencies across global markets. This dual design allows the study to systematically present the technical requirements, submission processes, and review mechanisms, while also drawing cross-regional comparisons to highlight areas of harmonization and divergence.

Data Sources [24-30]

The study is based primarily on **secondary data sources**, which provide reliable, validated information on regulatory practices and eCTD requirements. The following data sources were used:

Data Collection Strategy

The research employed a purposeful sampling strategy to identify and analyze documents most relevant to the study's focus on regulatory practices and electronic Common Technical Document (eCTD) requirements. Sources were grouped into four primary categories:

Regulatory Authority Guidelines

- Official publications from leading regulatory authorities were collected, including the U.S. Food and Drug Administration (USFDA), European Medicines Agency (EMA), Pharmaceuticals and Medical Devices Agency (PMDA, Japan), Health Canada, and the Central Drugs Standard Control Organization (CDSCO, India).
- These documents provided technical and procedural details on dossier compilation, submission pathways, validation criteria, and country-specific deviations from the ICH standards.
- Examples include the USFDA Guidance on eCTD Submissions, EMA's "eSubmission Roadmap," and CDSCO's eCTD pilot project circulars.

ICH Documentation

International Conference on Harmonisation (ICH) guidelines formed the core harmonization framework for analysis.

Key references included:

- ICH M4: detailing the Common Technical Document (CTD) structure across Modules 1–5.

- ICH M8: outlining eCTD technical specifications, submission granularity, and electronic validation criteria.
- These guidelines were critical for comparing regional adaptations against the harmonized baseline.

Published Research

- Peer-reviewed journal articles from databases such as Science Direct, PubMed, and Springer L ink were reviewed to capture scholarly perspectives on eCTD adoption, implementation challenges, and regulatory harmonization.
- Industry white papers and regulatory intelligence reports (e.g., from DIA, RAPS, or consulting firms) were also analyzed to supplement academic literature with practical insights and trend analyses. This category helped bridge the gap between prescriptive requirements and observed industry practices.

Case Studies and Secondary Reports

- Practical experiences of pharmaceutical companies, as documented in conference proceedings, regulatory workshops, and consultancy case studies, were included. Reports highlighting regional differences in eCTD adoption timelines, validation failure case studies, and industry readiness assessments provided applied perspectives. These case studies enabled the study to assess not only compliance requirements but also operational challenges and strategic considerations for industry stakeholders.

Data Analysis Approach

The collected documents were analyzed using a comparative qualitative content analysis method. The following steps were applied:

Document Coding and Categorization

- Each source was coded according to thematic categories: structural requirements (Modules 1–5), technical specifications, regional variations, implementation challenges, harmonization initiatives.
- Coding allowed systematic comparison across regions (US, EU, Japan, Canada, India) and against ICH baseline standards.

Triangulation for Validation

- To ensure accuracy, each regulatory requirement was validated against at least two independent sources (e.g., an FDA guidance document cross-verified with an ICH technical specification or EMA roadmap).
- Triangulation minimized interpretive bias and enhanced the reliability of findings.

Comparative Mapping

- Regulatory requirements were mapped against the ICH M4/M8 framework to identify convergence (areas of harmonization) and divergence (region-specific deviations).
- A cross-regional matrix was developed to visualize procedural differences and highlight barriers to global harmonization.

Synthesis and Interpretation

- Findings were synthesized into narrative themes, linking regulatory prescriptions with practical challenges.
- Patterns such as *timeline differences, validation tool adoption, and dossier lifecycle management* were highlighted to generate insights relevant to both regulators and industry stakeholders.

Methodological Rigor and Limitations

To maintain methodological rigor, the study applied dual verification, consistency checks, and conservative interpretation of ambiguous regulatory provisions. An audit trail of coding decisions and comparative matrices was maintained for transparency. However, the reliance on secondary data introduces certain limitations. Not all regulatory experiences (e.g., unpublished industry struggles or region-specific pilot outcomes) are documented in open sources. Additionally, while secondary data ensures validated information, it may lag behind real-time regulatory updates, especially in fast-evolving jurisdictions such as India's CDSCO. These limitations were mitigated by prioritizing most recent official documents and cross-verifying with multiple secondary analyses.

Table.1: Data Sources for the Study

Source	Examples	Purpose
Regulatory Authority Sites	USFDA (21 CFR, ESG guidance), EMA (CESP guidance), PMDA (JP M1), CDSCO pilot	Extracting official requirements and procedures for eCTD submissions.
ICH Documentation	ICH M4 (CTD), ICH M8 (eCTD specifications v3.2.2, v4.0 roadmap)	Understanding global harmonization framework.
Published Literature	Research papers, reviews, white papers	Insights on technical challenges, benefits, and comparative perspectives.
Case Studies / Industry Data	Reports from multinational submissions, validation errors, lifecycle tracking	Real-world examples of successful/failed submissions and lessons learned.

Data Collection Methods

Data collection for this study was conducted using a systematic review methodology, which ensured that information gathered was comprehensive, reliable, and reproducible. The systematic review process followed a structured protocol: (i) identification of sources, (ii) screening for relevance, (iii) detailed extraction of regulatory requirements, and (iv) synthesis and comparative analysis. This approach minimized bias and ensured that both formal regulatory requirements and practical industry experiences were incorporated.

Systematic Review of Regulatory Guidelines

The primary data set was drawn from official regulatory authority publications. The systematic review covered guidance documents, procedural manuals, technical specifications, and notices issued by the following agencies:

- U.S. Food and Drug Administration (USFDA)
- European Medicines Agency (EMA)

- Pharmaceuticals and Medical Devices Agency (PMDA, Japan)
- Health Canada
- Central Drugs Standard Control Organization (CDSCO, India)

Within these publications, the review focused on three key domains:

- **Module 1 Regional Requirements**: Jurisdiction-specific administrative, labeling, and regional dossier content.
- **Technical Validation Specifications**: eCTD granularity, file formats, lifecycle management, and validation criteria.
- **Submission and Review Processes**: Procedures for dossier submission, validation workflows, and timelines for regulatory review.

Each document was screened to ensure recency and relevance, with priority given to the latest official versions (e.g., FDA eCTD Guidance, EMA eSubmission Roadmap, CDSCO Medical Device Rules updates). Extracted information was coded thematically for cross-jurisdictional comparison.

2. Secondary Reports

To complement regulatory texts, secondary data sources were systematically identified and reviewed. These included:

- Industry reports and white papers from professional associations (e.g., DIA, RAPS) and regulatory intelligence providers.
- Case studies and consultancy reports detailing pharmaceutical company experiences with eCTD submissions in different jurisdictions.
- Surveys and benchmarking studies that assessed industry readiness, submission timelines, and common causes of validation failures.

These secondary reports provided practical insights into implementation challenges, compliance strategies, and outcome patterns, which were not always captured in official documents. Findings were triangulated with regulatory sources to ensure consistency.

Interviews

Where possible, semi-structured interviews with regulatory affairs professionals and industry experts were conducted to gain firsthand perspectives. The interviews were guided by a flexible question set focusing on:

- Experiences with eCTD submission processes.
- Common challenges encountered (technical validation errors, differing regional expectations).
- Strategies for compliance and regulatory interactions.

All interview responses were anonymized, transcribed, and analyzed using qualitative coding techniques. Themes were compared with findings from documentary sources to enhance depth and contextual understanding. While optional, this step added experiential evidence to the study, bridging the gap between regulatory theory and practice.

Data Analysis

The collected data were subjected to a comparative qualitative content analysis. The process involved:

1. Coding of Extracted Information: Categorizing regulatory requirements, validation specifications, and process descriptions under predefined themes.
2. Triangulation: Cross-validating insights from regulatory guidelines, secondary reports, and interviews to ensure reliability.
3. Comparative Mapping: Aligning regional practices against the ICH M4 (CTD structure) and ICH M8 (eCTD specifications) to identify convergence and divergence.
4. Synthesis: Developing a narrative that highlights patterns, gaps, and regulatory harmonization opportunities across jurisdictions.

Methodological Rigor

To ensure robustness, the methodology adhered to the following principles:

- **Transparency**: All sources were archived, with coding and analysis steps documented in an audit trail.
- **Validity**: Requirements were verified against at least two independent sources wherever possible.
- **Conservative Interpretation**: Ambiguities were resolved in favor of regulator-aligned interpretations.
- **Reproducibility**: The systematic review protocol ensures that future researchers could replicate the data collection and analysis process.

Table.2: Data Collection Strategy

Method	Details	Expected Outcome
Systematic review of guidelines	USFDA, EMA, PMDA, Health Canada, CDSCO documentation	Extract regulatory and technical submission criteria.
Literature review	Journals, books, and regulatory reports	Identify harmonization trends and technical gaps.
Case study analysis	Selected examples of eCTD submissions	Provide real-world context to regulatory requirements.
Interviews/secondary perspectives*	Insights from regulatory experts (if available)	Validate findings and highlight industry practices.

(*optional, depending on availability)

Data Analysis

The collected data were analyzed using a comparative and thematic framework, integrating structured matrices, process mapping, and qualitative content analysis. This approach allowed both a systematic comparison of regulatory requirements and an interpretive synthesis of broader themes and challenges.

1. Comparative Matrix Development

A comparative matrix was constructed to align regulatory requirements from the USFDA, EMA, PMDA (Japan), Health Canada, and CDSCO (India). The process followed three steps:

1. Data Extraction: Key requirements were extracted from regulatory authority guidelines, ICH specifications, and validated secondary sources.
2. Tabular Alignment: Requirements were arranged side by side to allow direct comparison across jurisdictions.
3. Categorization of Parameters: The matrix emphasized specific focus areas, including:

- Module 1 regional specifications (administrative and country-specific content).
- XML backbone differences (technical structures for eCTD submissions).
- Validation requirements (software checks, error thresholds, file formats).
- Review timelines (statutory or target performance goals).

This method facilitated the identification of convergences (harmonized elements) and divergences (regional deviations), providing a structured foundation for later interpretation.

Flowchart Construction

To visually represent procedural steps, flow diagrams were developed for submission and review processes. Flowcharts were created using a standardized graphical notation (rectangles for processes, diamonds for decisions, arrows for sequencing). Two categories of pathways were mapped:

Submission and Review Workflow: Compilation → Validation → Submission → Review → Approval. This pathway captured the stepwise process common across agencies, with regional variations highlighted (e.g., FDA's automated validation vs. CDSCO's manual review stages). Lifecycle Management of Variations and Amendments: Flow diagrams were also developed to depict processes for handling post-approval changes, such as minor variations, major amendments, and supplemental filings. These diagrams highlighted differences in classification of variations, review timelines, and resubmission requirements across jurisdictions. The flowchart method provided a clear, visual representation of procedural complexity and regulatory logic, aiding comparative interpretation.

3. Qualitative Thematic Analysis

Finally, a qualitative thematic analysis was applied to synthesize insights across regulatory texts, secondary reports, and case studies. The process involved:

1. Coding: Extracted text was coded into thematic categories (e.g., "harmonization," "validation errors," "review delays").
2. Pattern Identification: Codes were grouped into higher-order themes, enabling recognition of commonalities and differences across regions.
3. Interpretation: Key themes were elaborated with contextual detail, such as:

- Harmonization Challenges: Persistent differences in Module 1 structures and XML backbones despite ICH guidance.
- Frequent Validation Errors: Industry reports highlighting recurring technical issues (e.g., missing hyperlinks, incorrect granularity).
- Review Delays: Bottlenecks due to NB capacity constraints (EU) or evolving digital infrastructure (India)
- The thematic analysis ensured that the study went beyond procedural comparisons to address systemic trends, implementation barriers, and regulatory evolution.

Results and Discussion

Comparative Analysis of Country-Specific eCTD Requirements: The comparative analysis of eCTD guidelines across major regulatory authorities reveals that Modules 2–5 are largely harmonized, reflecting the success of the ICH initiative in standardizing dossier structures for quality, non-clinical, and clinical data. Across the USFDA, EMA, PMDA, Health Canada, and CDSCO, Modules 2 through 5 show negligible variation, ensuring that sponsors can prepare the majority of their submissions in a globally consistent manner.

However, significant divergences are observed in Module 1, which contains administrative and region-specific information. This is consistent with the expectation that Module 1 lies outside the scope of ICH harmonization and remains under the jurisdiction of individual regulatory authorities.

Module 1: Regional Variations

- USFDA: Requires detailed forms, labeling information, and patent certification data, reflecting the U.S. emphasis on intellectual property considerations and structured regulatory forms.
- EMA (EU): Module 1 includes EU-specific forms, Summary of Product Characteristics (SmPC), Package Information Leaflet (PIL), and country-specific annexes. This reflects the decentralized nature of EU approvals, where central guidance coexists with member state obligations.
- PMDA (Japan): Distinctive features include the requirement for Japanese translations within Module 1, adding a linguistic dimension to submission complexity.
- Health Canada: Incorporates regional forms, labeling, and a Quality Overall Summary (QOS) with slight structural variations compared to the ICH format.
- CDSCO (India): Currently in a pilot stage, using hybrid submissions that combine paper and electronic elements. Regional forms remain central, and alignment with ICH modules is ongoing rather than fully implemented.

The analysis indicates that Module 1 continues to represent the primary barrier to full global harmonization, as it reflects not only regulatory culture but also legal, linguistic, and administrative requirements unique to each region.

Modules 2–5: Global Harmonization

Across all five agencies, **Modules 2–5** remain fully aligned with the ICH CTD framework:

- **Module 2** provides standardized summaries (Quality Overall Summary, Non-clinical Overview, Clinical Overview).
- **Module 3** addresses quality/CMC requirements, ensuring consistency in chemistry, manufacturing, and controls.
- **Modules 4 and 5** present non-clinical and clinical study reports in an identical format across all jurisdictions.

This harmonization significantly reduces duplication of effort for multinational companies, as core scientific data can be repurposed with minimal adjustments.

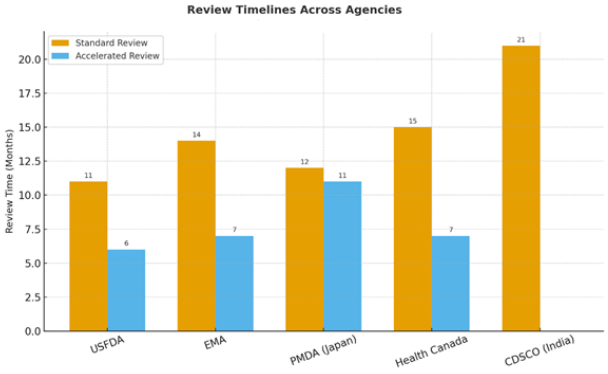

Fig.3: Review timelines across agencies

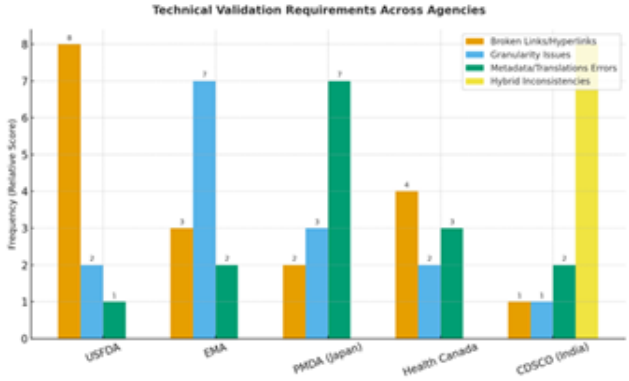

Fig.4 Technical Validation requirements across agencies

Technical Validation Requirements across Agencies

The analysis of technical validation requirements shows clear variation across regulatory agencies, reflecting differences in digital infrastructure maturity, dossier specifications, and submission practices.

- **USFDA**: Exhibits the highest frequency of broken links and hyperlink errors (score = 8), underscoring the strict reliance on robust internal hyperlinking within the eCTD. Minor issues were also observed in granularity (2) and metadata (1), though less significant than hyperlink errors.
- **EMA (EU)**: Validation failures are most frequently associated with granularity issues (7), indicating challenges in correctly segmenting documents according to EMA's detailed granularity requirements. Broken links (3) and metadata errors (2) occur less frequently.
- **PMDA (Japan)**: Shows a high incidence of metadata and translation errors (7), reflecting the linguistic and formatting complexities of Japanese submissions. Moderate issues include granularity (3) and broken links (2).
- **Health Canada**: Demonstrates a balanced profile with moderate frequencies of broken links (4), granularity errors (2), and metadata inconsistencies (3). This suggests a relatively stable system with no single dominant validation issue.
- **CDSCO (India)**: Unlike other regions, the most frequent issue is hybrid inconsistencies (7), arising from the country's ongoing transition between paper-based and electronic submissions. Minor occurrences of broken links (1), granularity (1), and metadata errors (2) were also noted.

Case Study Findings

Case Study 1: USFDA Submission

A multinational pharmaceutical company submitted a New Drug Application (NDA) to the USFDA in the full eCTD format. The dossier underwent pre-validation using GlobalSubmit VALIDATE, which flagged minor hyperlinking issues. These were corrected before final transmission through the Electronic Submissions Gateway (ESG).

- Outcome: Submission accepted without technical rejection.
- Challenges: Hyperlink integrity issues, a common problem in US submissions.
- Lesson Learned: Early use of validation tools reduces the risk of rejection and ensures compliance with USFDA's strict technical standards.

Case Study 2: EMA Submission

A European biotech company submitted a centralized procedure application to EMA via the Common European Submission Portal (CESP). Unlike the USFDA case, the dossier encountered initial validation failures related to granularity inconsistencies in Module 3 (Quality).

- Outcome: Validation failure caused a two-week delay before corrections were resubmitted and review could begin.
- Challenges: Inconsistent splitting of Quality documentation that did not align with EMA's strict granularity requirements.
- Lesson Learned: Granularity rules vary regionally and must be meticulously followed to prevent delays in the review process.

Comparative Discussion

The two case studies demonstrate the regional variability in validation priorities despite global reliance on the eCTD format:

1. **USFDA:** Focuses heavily on hyperlink integrity, where broken or incorrect links pose the most significant risk to dossier acceptance.
2. **EMA:** Prioritizes granularity compliance, especially in Module 3 (CMC data), where misalignment directly impacts the review timeline.
3. **Broader Implication:** Even though Modules 2–5 are harmonized under ICH, technical and administrative requirements in Module 1 and validation rules diverge significantly across regions. This necessitates region-specific submission strategies for successful global filings.

Cross-Case Lessons

From the two case studies, several shared best practices emerge that can guide sponsors preparing eCTD submissions across multiple jurisdictions:

1. **Proactive Pre-Validation:** Early and repeated use of validation tools (e.g., GlobalSubmit VALIDATE,

EMA's eValidator) allows technical issues to be identified and corrected before official submission.

2. **Region-Specific Compliance:** Agencies differ in their technical priorities—hyperlink robustness for the USFDA, granularity rules for the EMA, metadata accuracy for PMDA, and hybrid handling for CDSCO. Tailoring validation checks to these priorities reduces rejection risk.
3. **Internal Audit Trails:** Maintaining documented records of validation runs, corrections, and coding decisions ensures traceability and accountability, supporting both compliance and audit readiness.
4. **Submission Readiness Reviews:** Conducting internal readiness checks, ideally by cross-functional regulatory teams, ensures that both scientific content and technical structure align with regional expectations.
5. **Time Buffering in Project Planning:** Given that validation issues can delay reviews (as seen in the EMA case), regulatory project plans should include contingency timelines to account for unexpected re-submissions.

Discussion

Interpretation of Results

The comparative analysis of eCTD requirements across regulatory authorities (USFDA, EMA, PMDA, Health Canada, and CDSCO) revealed both convergence and divergence in dossier preparation and review. Modules 2–5 follow ICH standards consistently, ensuring that quality, non-clinical, and clinical data remain uniform. However, Module 1 demonstrates significant regional variation, leading to additional workload for companies pursuing global submissions. For instance, USFDA requires patent certification data, EMA emphasizes country-specific annexes, and PMDA requires Japanese translations. These differences, though regionally justified, reduce the harmonization that eCTD was intended to promote. Moreover, technical validation requirements especially XML granularity and hyperlinking vary slightly, further complicating multinational submissions. Thus, the similarities facilitate a shared foundation for global submissions, but the differences create duplication, potential delays, and higher compliance costs.

Challenges in eCTD Preparation

The transition from paper-based dossiers to eCTD has reduced logistical burdens but introduced **technical challenges**.

- **Formatting Issues**: Inconsistent PDF formats, incorrect bookmarks, and broken hyperlinks are frequent causes of technical rejection.
- **Lifecycle Management**: Companies often face difficulties in handling variations, supplements, and renewals due to lack of harmonization in update protocols.
- **Validation Errors**: Validation tools vary across agencies, and dossiers compliant in one region may be flagged in another.

Table 3: Challenges in eCTD Preparation

Challenge	Description	Impact
Technical Formatting	Broken hyperlinks, missing bookmarks, incorrect file names	Causes submission rejection or delay
Lifecycle Management	Difficulty in updating variations across multiple agencies	Duplication of effort, inconsistent dossiers
Validation Tool Variability	Different agencies use different validation rules and tools	Risk of regional rejection despite ICH compliance
Resource Constraints	High cost of eCTD software and training, esp. for SMEs	Barrier to adoption in emerging markets

Challenges in Regulatory Review

Even when technically compliant, eCTDs may face challenges during regulatory review.

- **Inconsistency in Module 1 Requirements**: Each agency requires region-specific forms, certificates, and labeling documents.
- **Country-Specific XML Granularity**: The level of document splitting differs, with EMA requiring finer granularity compared to USFDA.
- **Regulatory Queries**: Agencies may raise different queries for the same dossier, prolonging review timelines.

Table 4: Challenges in Regulatory Review

Agency	Key Challenge	Impact on Review
USFDA	ESG-specific XML validation	Technical rejections if XML backbone not compliant
EMA	Stringent granularity requirements	Additional dossier splitting; delays if unmet
PMDA	Mandatory Japanese translations	Longer preparation times for global submissions
Health Canada	REP-based lifecycle updates	Misalignment with global lifecycle tracking
CDSCO (India)	Pilot-phase hybrid submissions	Delayed adoption; longer review timelines

Benefits of eCTD

Despite challenges, eCTD adoption has provided significant **efficiency and transparency benefits** for both regulators and applicants.

- **Faster Review Timelines**: Agencies report shorter timelines due to automated navigation and validation.
- **Improved Lifecycle Tracking**: eCTD supports seamless updates for variations, renewals, and responses.
- **Global Competitiveness**: Adoption of eCTD strengthens international credibility and accelerates patient access to therapies.

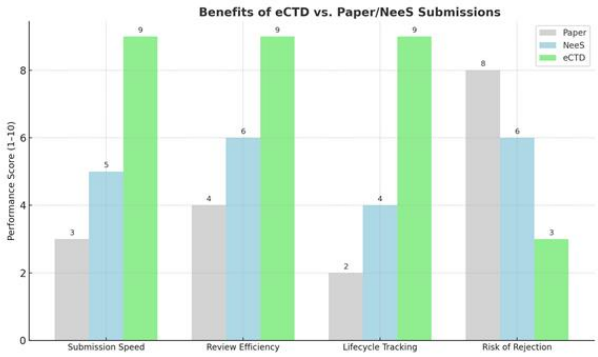

Fig.5: Benefits of eCTD vs Paper / NeeS Submission

Future Perspectives

The evolution of eCTD is ongoing, with eCTD v4.0 being the next milestone. Based on HL7 RPS (Regulated Product

Submission) standard, v4.0 introduces greater interoperability, flexibility in lifecycle management, and improved reviewer navigation. Global agencies are gradually piloting its implementation, with full adoption expected within the next decade. Additionally, global harmonization initiatives are essential. Agencies under ICH are working to minimize regional differences in Module 1, while WHO encourages adoption in emerging markets. Finally, AI-based dossier review systems are expected to revolutionize regulatory science. AI could assist in automating dossier screening, identifying inconsistencies, and even predicting review timelines. This technological integration will not only accelerate approvals but also reduce human error.

Table 5: Future Perspectives in eCTD Submissions

Future Direction	Description	Expected Impact
eCTD v4.0 Implementation	HL7 RPS-based standard with enhanced interoperability	Greater harmonization and flexibility in submissions
Global Harmonization Initiatives	Regulatory convergence under ICH and WHO initiatives	Reduced duplication, faster global approvals
AI-Based Review Systems	Use of AI to automate dossier review and lifecycle management	Shorter timelines, improved accuracy

Conclusion

This work set out to provide a comparative analysis of medical device regulatory pathways in the United States (USFDA), the European Union (EU MDR), and India (CDSCO). By systematically examining classification systems, pre-market approval routes, dossier requirements, quality system obligations, UDI traceability, and post-market surveillance, the study has produced a structured view of both convergence trends and divergences with practical consequences.

Findings

Convergence

All three systems are gravitating toward a risk-based lifecycle approach anchored in ISO 13485-aligned QMS, unique device identification (UDI) frameworks, and increasing reliance on post-market surveillance and real-world evidence.

Divergences

- US vs EU: Predicate-based 510(k) contrasts with the EU's CER/PMCF model, while the De Novo pathway has no direct EU equivalent.
- EU vs India: The EU mandates PRRC and prescriptive economic operator regimes, whereas India's MDR 2017 is still expanding its oversight through guidance and MvPI.
- US vs India: Predictable statutory review clocks in the US are absent in India, where practical timelines remain variable.

Operational Impacts.

Manufacturers face tangible bottlenecks in Notified Body capacity in the EU and site audit/resource dependencies in India, while the US provides relatively predictable review timelines but still demands rigorous predicate or PMA evidence.

Strategic Implications

For manufacturers targeting multi-region submissions, the findings support several best practices:

- Early classification alignment across jurisdictions, especially for novel software/active devices.
- Integrated evidence ladders that can be modularized across submissions.
- QMS harmonization to ISO 13485 with FDA-specific deltas addressed in advance of QMSR 2026.
- Documentation crosswalks linking DHF content to 510(k)/PMA, Annex II/III TD, and India DMF/PMF.
- Proactive UDI data governance to serve both GUDID and EUDAMED.
- Resource buffers to accommodate EU NB scheduling and India's evolving infrastructure.

Limitations

The study acknowledges that jurisdictional guidance is continuously evolving, and that timelines vary by product complexity, dossier quality, and regulatory interactions. Thus, while the comparative framework is robust as of September 2025, it requires ongoing monitoring.

Closing Statement

In sum, while the US, EU, and India share a common trajectory of risk-based, lifecycle-oriented regulation, the differences in evidentiary expectations, operator responsibilities, and review timelines continue to pose strategic challenges. A harmonized, proactive approach—centered on ISO 13485, strong evidence generation, and living documentation frameworks—offers the best pathway to regulatory success, faster market access, and enhanced patient safety.

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AI Tool Declaration

The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

Conflict of Interests

The authors declare no conflict of interest

Data Availability

Data will be available on request

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